

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Imazapic

Chemical Code # 5911, Tolerance # 52981

28 April 2005
Revised: 15 June 2005

I. DATA GAP STATUS

Combined, rat::	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat::	No data gap, no adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	Not required

Toxicology one-liners are attached.

All record numbers through 218273 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study in review.

File name: T050615

Prepared by H. Green, 4/28/05

Revised by T. Moore, 6/15/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****52981-0034** 213109, "AC 263,222: A Chronic Dietary Oncogenicity and Toxicity Study in the Albino Rat", (Joel E. Fischer, American Cyanamid Company, Agricultural Research Division, Princeton, NJ., and Pathology Associates, Inc., Frederick, MD., Laboratory Project No. Study T-0356, Toxicology Report No. AX93-3, 29 June 1994). 65 CD[®] [CrI:CD[®](SD)BR] rats per sex per group received AC 263,222 (96.4% imazapic) in the diet at 0 (basal diet), 5,000, 10,000, and 20,000 ppm for 24 months. 10 per sex per group were necropsied at 12 months. Mean daily intake of AC 263,222 was 253 ± 106 , 505 ± 212 , and 1029 ± 432 mg/kg/day for males and 308 ± 97 , 609 ± 185 , and 1237 ± 370 mg/kg/day for females at 5,000, 10,000, and 20,000 ppm respectively. There was no treatment-related effect on survival. At study termination, survival was 36%, 19%, 34%, and 31% for males and 46%, 35%, 39%, and 48% for females at 0, 5,000, 10,000, and 20,000 ppm respectively. Bodyweight, bodyweight gain, food consumption, hematology, and urinalysis for treated groups were generally comparable to control values during the 24-month study period. Serum chemistry parameters were generally comparable to controls. Slight intermittent increases in cholesterol unrelated to treatment were recorded at the mid (females) and high (males) dose levels. Gross pathology and organ weights were unremarkable. Neoplastic findings at the high dose level included slightly increased incidence of thyroid C-cell neoplasms in males and of uterine endometrial stromal polyps in females at terminal sacrifice. No statistical significance was found when compared with control groups and the incidence was reported to be within the historical control range. Additionally, the morphology and differentiation of the neoplasms were similar in control and treated animals. No evidence of oncogenicity. Chronic NOEL \geq 20,000 ppm (1029 ± 432 mg/kg/day (males) and 1237 ± 370 mg/kg/day (females)). No Adverse effect. Acceptable. (Green and Gee, 3/11/05).

****52981-0031** 213099, "AC 263,222: A 13-Week Dietary Toxicity Study in the Albino Rat", (Joel Fischer, American Cyanamid Company, Agricultural Research Division, Princeton, NJ., Study No. L-2293, American Cyanamid No. AX92-2, 30 September 1992). 20 CD[®] [CrI:CD[®](SD)] rats per sex per group received AC 263,222 (93.7% imazapic) in the diet at 0 (basal diet), 5,000, 10,000, and 20,000 ppm for 13 weeks. Average test article intake for males and females was 408, 804, and 1625 mg/kg/day at 5,000, 10,000, and 20,000 ppm respectively during the 13-week treatment period. No deaths. Food consumption was significantly increased for males at 5,000, 10,000, and 20,000 ppm and for females at 10,000 ppm during the first week of the study. During the remainder of the study, food consumption for treated groups was comparable to controls. Bodyweights were slightly increased (not statistically significant) for males at 5,000 and 10,000 ppm during the 13-week study period. Bodyweights for females in all treated groups and for males at 20,000 ppm were comparable to controls over the entire study period. Bodyweight gains for treated groups (both sexes) over the 13-week period were generally comparable to controls. No treatment-related findings were noted for hematology, serum chemistry, urinalysis, necropsy, organ weights, or histopathology. No ophthalmology. NOEL = 20,000 ppm (1625 mg/kg/day). No adverse effects. Acceptable. (Green and Gee, 3/10/05).

CHRONIC TOXICITY, DOG

****52981-0033** 213108, "A One-Year Dietary Toxicity Study of AC 263,222 in Dogs (Study 91117)". (S. Wolford, Wilbur G. Malcolm Toxicology Laboratory, Medical Research Division, American Cyanamid Division, Pearl River, NY., American Cyanamid No. 91117, 1 March 1993). Six Beagle dogs per sex per group received AC 263,222 (96.9% imazapic) in the diet at 0 (basal diet), 5,000, 20,000, and 40,000 ppm for 1 year. Average compound consumption during the study was 137.4, 500.7, and 1140.8 mg/kg/day for males and 180.2, 533.8, and 1092.1 mg/kg/day for females at 5,000; 20,000; and 40,000 ppm respectively. One male died from

bronchopneumonia at 40,000 ppm on day 233. An increase in salivation was noted at 20,000 ppm and at 40,000 ppm. Emesis (incidence per animal) was increased for both sexes at 40,000 ppm. Food consumption was decreased at some intervals at 20,000 (females) and 40,000 ppm (both sexes). Overall bodyweight gain was decreased at 40,000 ppm in both sexes. At 5,000 ppm, clinical signs, food consumption, and bodyweight were comparable to controls. Statistically significant changes were noted for hematology. Mean hematocrit and hemoglobin were decreased in males on days 35 and 91 at 20,000 and on days 35, 42, 91, 173, and 357 at 40,000 ppm. Erythrocytes were decreased for females at 5,000 ppm (days 35, 91, and 173), 20,000 ppm (day 91), and 40,000 ppm (days 35, 42, 91, and 173), and for high dose males on days 35, 42, 91, 173, and 357. Mean corpuscular volume and mean corpuscular hemoglobin were decreased in males at 5,000 ppm (day 35), 20,000 ppm (days 91 and 173), and 40,000 ppm (days 35, 42, 91, 173, 357) and, in females, at 40,000 ppm (days 91, 173, and 357). Mean corpuscular hemoglobin concentration was decreased at 40,000 ppm for males (days 91, 173, and 357) and females (days 35, 42, 91, 173, and 357). Statistically significant treatment-related serum chemistry changes were recorded at 40,000 ppm. Increases were seen in serum potassium (days 91 and 173 in males and days 173 and 357 in females), phosphorus (days 35 and 173 in males and days 35, 42, 91, 173, and 357 in females), lactate dehydrogenase (days 35 and 91 in males and days 35, 91, and 173 in females), creatinine kinase (days 35 and 42 in both sexes, day 357 in males), aspartate aminotransferase (days 35 and 42 in both sexes), and alanine aminotransferase (days 35, 42, 91, and 173 in both sexes). Decreases in albumin (days 35 and 42 in males and days 35, 42, and 91 in females) were also noted. Urine volume and water intake were significantly decreased for males on days 176-178 and 351-353 at 20,000 and 40,000 ppm. Necropsy revealed gelatinous, red bone marrow in 3 males and all females at 40,000 ppm. Group mean absolute and relative liver weights were significantly increased for both sexes at 40,000 ppm. Microscopy indicated skeletal muscle degeneration (minimal severity) with lymphocyte and macrophage infiltration (minimal) in abdominal and vastus muscle of 3/6 males at 5,000 ppm (not in all of the same animals). 1/6 females had skeletal muscle degeneration in abdominal and vastus muscles. Skeletal myopathy of minimal severity was reported focally in only a few fibers per tissue section. Additionally, 2/6 females had minimal lymphocytic and macrophage infiltrations, one in the vastus muscle and the other in the diaphragm. At 20,000 ppm, skeletal muscle degeneration (minimal) with lymphocytic and macrophage infiltration (minimal) was present in 3/6 (vastus muscle) and 4/6 males (abdominal muscle). In females, 2/6 (vastus and abdominal muscle) had skeletal muscle degeneration (minimal) and 6/6 (vastus) and 5/6 (abdominal) had lymphocytic and macrophage infiltration (minimal). Minimal mononuclear inflammatory cell (lymphocytes and macrophages) infiltration of affected muscles was present in all animals. Two males and one female had a slight increase in bone marrow erythropoiesis. Extramedullary erythropoiesis in the spleen of one of the males was also noted. At 40,000 ppm, minimal to moderate skeletal muscle degeneration was noted in 5/6 (vastus) and 4/6 (abdominal) females and 4/5 males (vastus and abdominal). Mononuclear inflammatory cell infiltration was slight to moderate. Bone marrow erythropoiesis (slight to moderate) was increased in most animals accompanied by a slight increase in extramedullary erythropoiesis in the spleen (4/5 males, 2/6 females). Chronic NOEL < 5,000 ppm (137.4 mg/kg/day for males and 180.2 mg/kg/day for females) (skeletal muscle degeneration). Possible adverse effect: skeletal muscle degeneration with an associated inflammatory response (macrophage and lymphocytic infiltration). Acceptable. (Green and Gee, 3/10/05).

ONCOGENICITY, MOUSE

**52981-0035 213110, "A Chronic Dietary Toxicity and Oncogenicity Study in the Albino Mouse with AC 263,222", (Joel E. Fischer, American Cyanamid Company, Agricultural Research Division, Princeton, NJ., Report No. T-0391, Toxicology Report AX93-5, 17 June 1994). 65 CD®-1 [Crl(ICR)BR] mice per sex per group received AC 263,222 (96.9% imazapic) in the diet at 0 (basal diet); 1,750; 3,500; and 7,000 ppm for 18 months. 10 per sex per group were necropsied at 12 months. Mean daily intake of AC 263,222 was 271 ± 52 , 551 ± 104 , and 1134 ± 265 mg/kg/day for males and 369 ± 87 , 733 ± 184 , 1442 ± 348 mg/kg/day for females at 1,750, 3,500,

and 7,000 ppm respectively over the 18-month treatment period. Slight reductions in male bodyweight were noted through week 16, but bodyweight gain was unaffected through the 18 month study period and female bodyweight and bodyweight gain were comparable to controls. No treatment-related effects on survival, food consumption, hematology, gross pathology, organ weights, or histopathology were recorded. No evidence of oncogenicity. Chronic NOEL \geq 7,000 ppm. No adverse effects. Acceptable as an onco study only (no ophthalmology, urinalysis, or clinical chemistry). (Green and Gee, 3/10/05).

REPRODUCTION, RAT

**52981-0038 213113, "A Two-Generation (One-Litter) Reproduction Study with AC 263,222 in Rats", (Raymond E. Schroeder, Pharmaco LSR, Inc., Toxicology Services North America, East Millstone, NJ., Study No. 90-3639, 2 May 1994). 30 albino Crl:CD[®] BR (Sprague-Dawley derived) rats per sex per group received AC 263,222 (96.9% imazapic) in the diet at 0 (untreated diet), 5,000, 10,000, and 20,000 ppm through two generations (one litter per generation). Treatment began 14 weeks prior to mating. Test article intakes in mg/kg/day ranged from 236 to 578, 471 to 1226, and 935 to 2312 at the low, mid, and high-dose levels respectively (both sexes included, both generations) with means of 301 to 425, 605 to 884, and 1205 to 1703 mg/kg/day respectively. No treatment-related clinical observations or mortality were recorded for F0 and F1 animals. Mean weekly bodyweights for F1 females at initiation of premating treatment were higher than controls ($p \leq 0.05$) at 5,000 and 20,000 ppm (attributed to age differences). Mean bodyweight gains over the premating period were comparable to controls. Bodyweights for F1 males and F0 animals were comparable to controls throughout the study. Food consumption for F1 females was significantly reduced ($p \leq 0.01$, -6.0% to -11.2%) at 5,000 and 20,000 ppm during the first 3 weeks of the premating treatment period relative to controls. F1 male and F0 food consumption was generally comparable to controls throughout the study. F0 and F1 mating indices, pregnancy rates, gestation lengths, parturition data (mean live, dead, and total pups at birth), litter survival, and male fertility indices were comparable across groups. F1 and F2 pup weights were comparable to controls through lactation. F1 mean pup survival was slightly lower in treated groups for lactation days 0-4 (NS) compared to controls (97.1% vs 95.4%, 93.5% and 92% respectively). Pup survival indices were slightly lower than controls in the mid- and high-dose groups but not statistically significant for lactation days 4-21 (100% vs 93.6% and 95.5% respectively). The lower survival resulted from increased pup mortality in two litters in each group. Excluding these litters would result in survival of 97.7% and 98.4% respectively. Mean F2 pup survival was comparable to controls for lactation days 0-4 and 4-21. Parental and pup histopathology for both generations was unremarkable. Parental and Reproductive NOEL = 20,000 ppm (1205 to 1703 mg/kg/day). No adverse effect. No reproductive toxicity. Acceptable. (Green and Gee, 3/11/05).

TERATOLOGY, RAT

**52981-0036 213111, "Teratology Study with AC 263,222 in Rats", (James L. Schardein, International Research and Development Corporation, Mattawan, MI., IRDC study No. 141-030, American Cyanamid study No. 987-86-168, 18 November 1992). 25 mated female Charles River COBS[®] CD[®] rats per group received AC 263,222 (93.7% imazapic) by oral gavage at 0 (corn oil at 10 ml/kg), 250, 500, and 1000 mg/kg/day on gestation days 6 through 15. No maternal mortality or toxicity. Maternal appearance, behavior, bodyweight, and food consumption were similar across all groups. No indication of embryotoxicity or fetotoxicity. No adverse effect. No teratogenicity. Maternal and Developmental NOEL = 1000 mg/kg/day. Acceptable. (Green and Gee, 3/14/05).

TERATOLOGY, RABBIT

**52981-0037 213112, "A Teratology Study with AC 263,222 in Rabbits", (Karen M. MacKenzie, Hazleton Laboratories America, Inc., Madison, WI., HLA Study No. 6123-141, American

Cyanamid No. 987-86-170, 29 March 1992). 20 artificially inseminated female New Zealand White rabbits per group received AC 263,222 (93.7% imazapic) by oral gavage at 0 (0.4% carboxymethylcellulose in distilled water), 175, 350, 500, and 700 mg/kg/day on gestation days 7 through 19. One, 2, 4, 4, and 11 animals died at 0, 175, 350, 500, and 700 mg/kg/day respectively and 0, 2, 1, 1, and 1 were sacrificed *in extremis* respectively. All treated animals that died on test showed one or more of the following treatment-related symptoms/signs: oral discharge, nasal discharge, fluid-filled trachea and/or lungs, reddened trachea, and stomach lesions. Bodyweights for all treated groups were slightly lower (NS) than controls through gestation day 25 and comparable to, or greater than, controls on day 29. At 700 mg/kg/day, maternal bodyweight gains were significantly ($p \leq 0.05$) lower for gestation days 7 through 14 and 14 through 20, and significantly higher for days 25 through 29. Maternal food consumption was significantly lower ($p \leq 0.05$) for gestation days 9 through 19 at 700 mg/kg/day and on days 15 and 16 at 500 mg/kg/day. No treatment related fetal external observations, soft tissue abnormalities, or skeletal malformations. A significant increase ($p \leq 0.05$) in fetal incidence of rudimentary ribs was recorded at 350, 500, and 700 mg/kg/day. 18%, 24%, 36%, 32%, and 38% of fetuses had the variation at 0, 175, 350, 500, and 700 mg/kg/day respectively vs the reported historical control incidence of 22%. Litter incidence was generally comparable to vehicle control rates through 500 mg/kg/day. Maternal NOEL = 500 mg/kg/day (reduced food consumption and bodyweight gain, and increased mortality). Developmental NOEL = 700 mg/kg/day. No adverse effects. No teratogenicity. Acceptable. (Green and Gee, 3/14/04).

GENE MUTATION

**52981-0039 213114, "Evaluation of AC 263,222 in the Bacterial/Microsome Mutagenicity Test", (Karl A. Traul, American Cyanamid Company, Agricultural Research Division, Princeton, NJ, Study No. 115, 19 May 1992). Triplicate cultures of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and *Escherichia coli* strain WP2 uvrA⁻ were exposed (plate incorporation) to CL 263,222 (93.7% imazapic), in the presence and absence of activation (S9), at 0 (DMSO), 100, 500, 1000, 2500, and 5000 µg/plate for 48 hours. Assay was repeated. No increase in the mutation frequency was indicated. Acceptable. (Green and Gee, 3/14/05).

**52981-0039 213116, "CHO/HGPRT Forward Mutation Assay with AC 263,222", (Robert R. Young (original report), Maria A. Cifone (revised report), Hazleton Laboratories America, Inc., Kensington, MD, HWA study No. 9741-0-435, 26 May 1987, revised date - 24 April 1992). Chinese hamster ovary cells (CHO-K1-BH₄) (3×10^6 cells per tissue culture flask (75 cm²)) were exposed to AC 263,222 (93.7% imazapic), in the presence and absence of S9, at 0 (untreated medium), 0.5, 1.0, 2.0, 3.0, 3.5, 4.0, or 5.0 mg/ml for 4 hours. The pH of the 5 mg/ml stock was adjusted from ≤ 4.7 to pH 7.2-7.4 using NaOH. Two trials were conducted. Expression time was 7 days followed by plating in selection medium with 6 thioguanine, 2×10^5 cells per plate, 12 plates per culture for mutant selection. No increase in forward mutations. Acceptable. (Green and Gee, 3/14/05).

CHROMOSOME EFFECTS

**52981-0039 213115, "Evaluation of AC 263,222 in the *In Vitro* Chromosome Aberration Test in Chinese Hamster Ovary Cells", (Rajendar K. Sharma, American Cyanamid Company, Agricultural Research Division, Princeton, NJ, Study No. 86-11-001, 18 May 1992). Duplicate cultures of Chinese hamster ovary cells (CHO-WBL) were exposed to AC 263,222 (93.7% imazapic), in the presence and absence of S9 activation, at 0 (untreated medium), 0 (DMSO), 0.25, 1.0, 2.5, and 3.0 mg/ml. S9 activated cultures were exposed for 2 hours and non-activated cultures were exposed for 8 and 18 hours. Cells were arrested at 10 and 20 hours. No increase in structural chromosomal aberrations was indicated. Acceptable. (Green and Gee, 3/14/05).

**52981-0039 213117, "Chromosomal Aberration *In Vivo* in Mammalian Bone Marrow Cells with AC 263,222", (James L. Ivett, Hazleton Laboratories America, Inc., Kensington, MD., HLA Study

No. 9773-0-451, American Cyanamid No. 971-87-102, 24 April 1992). 15 Sprague-Dawley Crl:CD-BR rats per sex per group received a single oral gavage dose of AC 263,222 (93.7% imazapic) at 0 (corn oil), 500, 1667, and 5000 mg/kg. Bone marrow was harvested from 5 per sex per group at 6, 18, and 30 hours post-dosing. Fifty metaphase spreads were evaluated per animal and the mitotic index calculated from at least 500 cells. Two males at 5000 mg/kg in the 18 hour harvest group were found dead on the morning after dosing (attributed to dosing injury). One vehicle control female (30 hour harvest group) died within 5 minutes after colchicine administration. Soft stools were observed in all dose groups. No increase in structural chromosomal aberrations. Acceptable. (Green and Gee, 3/15/05)

DNA DAMAGE

52981-0040, -0051; 213119, 218273; "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures by Autoradiography", (A. Thilagar, SITEK Research Laboratories, Rockville, MD., SITEK Study No. 0051-5100, American Cyanamid No. 987-86-191, 28 May 1992). Primary hepatocytes (male Sprague-Dawley rats) were exposed to AC 263,222 (93.7% imazapic), in triplicate (2 ml of culture medium with 2.5×10^5 cells per ml), at 0 (WME), 0 (DMSO), 1000, 1500, 2000, and 2500 $\mu\text{g/ml}$ for 18 hours. 150 Nuclei per dose were counted in the autoradiography assay. **No adverse effect indicated.** No increase in the average net nuclear grain counts was indicated. Study previously unacceptable, upgradeable with submission of individual plate counts (nuclear counts, cytoplasm counts per coverslip); study data in vol. no. 52981-0051, rec. no. 218273 were sufficient to correct this deficiency; **Study acceptable.** (Green and Gee, 3/15/05, revised, Moore, 6/14/05).

METABOLISM

**52981-0040 213120, "CL 263,222: Metabolism of ^{14}C -CL 263,222 in the Rat", (Theresa Cheng, Hazleton Wisconsin, Inc., Madison, WI, Hazleton No. HWI 6123-169, American Cyanamid No. MET 93-008, 25 February 1993). 5 Crl:CD[®]BR rats per sex per group received a single dose of ^{14}C -CL 263,222 by oral gavage or intravenous injection at 10 or 1000 mg/kg. One group received 14 consecutive non-radiolabelled daily oral doses followed by one ^{14}C labelled oral dose (10 mg/kg). After dosing with radiolabel, animals were housed in individual metabolism cages and sacrificed 7 days later. Feces, urine, cage wash/rinse, cage wipes (methanol extracted), blood, fat, heart, spleen, ovaries, uterus, bone (femur), brain, kidney, liver, lungs, muscle (thigh), testes, and the residual carcass were analyzed for radioactivity by liquid scintillation counting (LSC). Metabolite profiles in urine, dissolved urine precipitate, and feces extract (ethyl ether) were determined using thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC). The major elimination route for dosed radioactivity was in urine. The mean percent of total dose (including cage wash and cage wipe) ranged from 94.0% to 102% (males) and 94.5% to 102% (females). The mean percent of total dose excreted in feces ranged from 0.79% to 3.44% (males) and 0.59% to 3.50% (females). The majority of radioactivity was excreted during 6 hours post-dosing.

Mean radioactivity concentrations in blood 7 days after a single dose at 10 mg/kg were not detectable. At 1000 mg/kg, concentrations were 0.127 ppm for males and <0.1 ppm for females. Mean radioactivity concentrations in tissues were generally not detectable (<0.01 ppm) at 10 and 1000 mg/kg. Residual radioactivity in the carcass ranged from <0.001 ppm to 0.043 ppm.

The unchanged test article, ^{14}C -CL 263,222, accounted for $\geq 93.5\%$ and $\geq 65.9\%$ of the total radioactivity in urine (94% to 102% of total administered dose) and feces (0.59% to 3.50% of total administered dose) respectively. Metabolites designated CL 303,459 and CL 263,284 (structural schematics were included) and several minor radioactive components were also detected in small amounts (< 5% combined of the total radioactivity in the sample). In feces, metabolites CL 303,459 (4.29% (males) to 5.38% (females) of radioactivity in the sample), CL 263,284 (1.96% (males) and 0.85% (females)), and CL 290,610 (0.69% (males) and 0.70% (females)) were

detected. The absolute amount of each of these corresponded to <0.2% of the administered dose. Several unknown metabolites accounted for less than 6% of total radioactivity in feces samples.

The proposed metabolic pathway of ^{14}C -CL 263,222 (see flow diagram with chemical structures, page 74) was based on components identified in the excreta. Oxidation of the methyl group on the pyridine ring of ^{14}C -CL 263,222 produced metabolite CL 263,284. The presence of CL 303,459 suggested the initial step of ring closure, reduction to intermediate CL 280,442, followed by hydrolysis to CL 303,459 and further hydrolysis to CL 290,610. Acceptable. (Green and Gee, 3/16/05).

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

**52981-0031 213099, "AC 263,222: A 13-Week Dietary Toxicity Study in the Albino Rat", (Joel Fischer, American Cyanamid Company, Agricultural Research Division, Princeton, NJ., Study No. L-2293, American Cyanamid No. AX92-2, 30 September 1992). 20 CD[®] [CrI:CD[®](SD)] rats per sex per group received AC 263,222 (93.7% imazapic) in the diet at 0 (basal diet), 5,000, 10,000, and 20,000 ppm for 13 weeks. Average test article intake for males and females was 408, 804, and 1625 mg/kg/day at 5,000, 10,000, and 20,000 ppm respectively during the 13-week treatment period. No deaths. Food consumption was significantly increased for males at 5,000, 10,000, and 20,000 ppm and for females at 10,000 ppm during the first week of the study. During the remainder of the study, food consumption for treated groups was comparable to controls. Bodyweights were slightly increased (not statistically significant) for males at 5,000 and 10,000 ppm during the 13-week study period. Bodyweights for females in all treated groups and for males at 20,000 ppm were comparable to controls over the entire study period. Bodyweight gains for treated groups (both sexes) over the 13-week period were generally comparable to controls. No treatment-related findings were noted for hematology, serum chemistry, urinalysis, necropsy, organ weights, or histopathology. No ophthalmology. NOEL = 20,000 ppm (1625 mg/kg/day). No adverse effects. Acceptable. (Green and Gee, 3/10/05).

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

0032; 213104; "Twenty-one Day Dermal Toxicity Study with AC 263,222, Lot #AC 5270-111 in Rabbits" (Moore, G.E., Biosearch Incorporated, Philadelphia, PA, Biosearch Project No. 87-5525A, American Cyanamid No. 971-87-103, 10/27/92). 822. AC 263,222 (Lot #AC 5270-111, purity = 93.7%) was mixed with saline and the resulting slurry was applied to the clipped skin of 6 New Zealand White rabbits per sex per dose at dose levels of 0 (saline), 250, 500, or 1000 mg/kg/day for 6 hours per day 5 days per week for 3 consecutive weeks using an occlusive dressing. No mortalities occurred. No treatment-related clinical signs were observed. No skin irritation was observed at the treatment sites. No effect on body weight was observed. Hematological and clinical chemistry investigations revealed no effects of biological significance. No effect on mean relative organ weights was observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested. **Acceptable.** (Corlett, 04/07/05)